

Crystallographic and Molecular Mechanics Study of Imidoxy Anticonvulsants

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Abstract

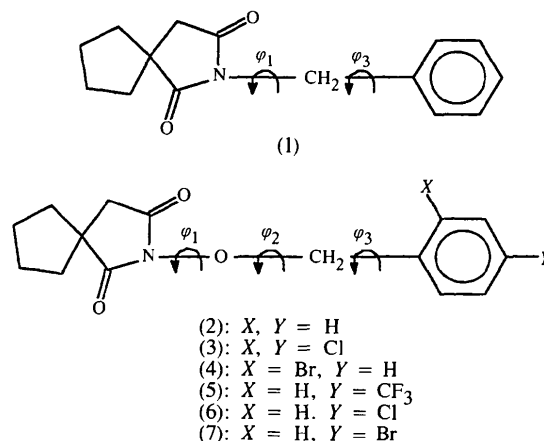
X-ray crystal structures have been determined of five compounds closely related to *N*-benzyl-2-azaspiro[4.4]nonane-1,3-dione (1), which is inactive as an anticonvulsant, and *N*-(benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (2), which is active. Conformational analyses have been carried out with (1), (2) and the new compounds *N*-(2',4'-dichlorobenzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (3), *N*-(2'-bromobenzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (4), *N*-(4'-(trifluoromethyl)benzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (5), which are all active anticonvulsants, and *N*-(4'-chlorobenzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (6) and *N*-(4'-bromobenzyloxy)-2-azaspiro[4.4]nonane-1,3-dione (7), which are inactive. Regardless of the substitution pattern, the conformations of compounds (2)–(7) in the crystals are very similar. Among the low-energy conformations, which are well distributed in the conformational space, that present in its solid state is dominant. *Ortho*-substitution considerably cuts down the number of conformations accessible within the set energy limit. The results of these studies alone do not explain the differences in activity.

1. Introduction

A series of 26 *N*-substituted 2-azaspiro[4.4]nonane-1,3-diones was studied for their ability to protect against maximal electroshock seizures [MES (Farrar, Ciechanowicz-Rutkowska, Grochowski, Serda, Pilati, Filippini, Hinko, El-Assadi, Moore, Edafiohgo, Andrews, Cory, Nicholson & Scott, 1993)]. They varied in their activity which, following the anticonvulsant screening project (ASP), was in the range 1 (the most active)–3 (inactive). It was concluded that although the general trend is for the activity to increase with increasing lipophilicity, steric and electronic effects must also be considered. Single crystal X-ray analyses carried out on (1) and (2) pointed to the possible importance of the orientation of the phenyl ring with respect to the heterocyclic ring; in the crystal structure the two rings are parallel (at 5.9°) in active (2), but almost perpendicular (at 102.4°) in inactive (1) (Farrar *et al.*, 1993). The

molecular conformation of both compounds is presented in Fig. 1.

The present work was undertaken in order to make a further study of the effect of phenyl substitution on the molecular conformation of (3)–(7) and to make a conformational analysis for (1)–(7) to search for any possible correlation between structure and activity in this series of compounds.



2. Experimental

2.1. X-ray studies

X-ray measurements were made using an Enraf-Nonius FAST area-detector diffractometer (Pflugrath & Messerschmitt, 1991) with graphite-monochromated Mo K α radiation following previously described procedures (Ciechanowicz-Rutkowska, Kieć-Kononowicz, Howard, Lieberman & Hursthouse, 1994) with setting parameters as given in Table 1.

The structures were solved by direct methods using SHELXS86 (Sheldrick, 1985) and refined with SHELXL93 (Sheldrick, 1993) employing full-matrix least-squares on F^2 . An empirical correction for absorption was made for structures containing chlorine and bromine using DIFABS (Walker & Stuart, 1983). Several reflections were omitted from the refinements, due to their being affected by the back stop shadow. All non-H atoms were refined anisotropically. At intermediate stages

Table 1. *Experimental details*

	(3)	(4)	(5)	(6)	(7)
Crystal data					
Chemical formula	C ₁₅ H ₁₅ Cl ₂ NO ₃	C ₁₅ H ₁₆ BrNO ₃	C ₁₆ H ₁₆ F ₃ NO ₃	C ₁₅ H ₁₆ ClNO ₃	C ₁₅ H ₁₆ BrNO ₃
Chemical formula weight	328.18	338.20	327.30	293.74	338.20
Cell setting	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	13.238 (1)	25.005 (5)	30.032 (3)	9.055 (5)	9.101 (2)
<i>b</i> (Å)	12.995 (1)	12.7399 (11)	12.0381 (13)	12.253 (10)	12.274 (2)
<i>c</i> (Å)	9.309 (4)	9.3636 (10)	9.099 (3)	26.855 (7)	27.270 (2)
β (°)	100.938 (13)	92.436 (9)	92.362 (15)	95.16 (3)	96.544 (12)
<i>V</i> (Å ³)	1572.3 (7)	2980.1 (7)	3286.8 (12)	2967.7 (29)	3026.4 (8)
<i>Z</i>	4	8	8	8	8
<i>D</i> _x (Mg m ⁻³)	1.386	1.508	1.323	1.315	1.485
Radiation type	Mo <i>K</i> α	Mo <i>K</i> α	Mo <i>K</i> α	Mo <i>K</i> α	Mo <i>K</i> α
Wavelength (Å)	0.71069	0.71069	0.71069	0.71069	0.71069
No. of reflections for cell parameters	250	250	250	250	250
θ range (°)	2–20	2–20	2–26	2–20	2–20
μ (mm ⁻¹)	0.421	2.765	0.113	0.264	2.723
Temperature (K)	293 (2)	293 (2)	293 (2)	293 (2)	293 (2)
Crystal form	Plates	Rods	Plates	Plates	Plates
Crystal size (mm)	0.3 × 0.2 × 0.1	0.30 × 0.16 × 0.08	0.32 × 0.28 × 0.05	0.6 × 0.6 × 0.05	0.36 × 0.20 × 0.10
Crystal colour	Colourless	Colourless	Colourless	Colourless	Colourless
DET (mm)†	39.84	39.93	39.88	39.86	39.77
θ (°)‡	–24.97	–24.97	–24.97	–24.97	–24.92
Time (s)§	15	15	15	10	15
Width (°)¶	0.20	0.20	0.20	0.20	0.20
Data collection					
Diffractometer	FAST diffractometer	FAST diffractometer	FAST diffractometer	FAST diffractometer	FAST diffractometer
Data collection method	<i>MADNES</i> (Pflugrath & Messerschmitt, 1991)	<i>MADNES</i> (Pflugrath & Messerschmitt, 1991)	<i>MADNES</i> (Pflugrath & Messerschmitt, 1991)	<i>MADNES</i> (Pflugrath & Messerschmitt, 1991)	<i>MADNES</i> (Pflugrath & Messerschmitt, 1991)
Absorption correction	Refined from ΔF (<i>DIFABS</i> ; Walker & Stuart, 1983)	Refined from ΔF (<i>DIFABS</i> ; Walker & Stuart, 1983)	None	Refined from ΔF (<i>DIFABS</i> ; Walker & Stuart, 1983)	Refined from ΔF (<i>DIFABS</i> ; Walker & Stuart, 1983)
<i>T</i> _{min}	0.873	0.742	–	0.649	0.491
<i>T</i> _{max}	1.141	1.264	–	1.636	0.955
No. of measured reflections	10 018	6935	5011	14 950	13 223
No. of independent reflections	3853	3650	2495	7632	7162
No. of observed reflections	1143	1016	529	1446	1286
Criterion for observed reflections	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)
<i>R</i> _{int}	0.0678	0.0534	0.0879	0.0760	0.0861
θ _{max} (°)	29.95	29.71	25.37	29.77	29.80
Range of <i>h</i> , <i>k</i> , <i>l</i>	–17 → <i>h</i> → 14 –13 → <i>k</i> → 17 –9 → <i>l</i> → 12	–32 → <i>h</i> → 20 –14 → <i>k</i> → 17 –12 → <i>l</i> → 12	–33 → <i>h</i> → 32 –10 → <i>k</i> → 13 –6 → <i>l</i> → 10	–12 → <i>h</i> → 12 –15 → <i>k</i> → 16 –35 → <i>l</i> → 23	–11 → <i>h</i> → 8 –7 → <i>k</i> → 16 –36 → <i>l</i> → 37
Refinement					
Refinement on	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²	<i>F</i> ²
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)]	0.0413	0.0599	0.0883	0.0483	0.0589
<i>wR</i> (<i>F</i> ²)	0.0947	0.1945	0.2703	0.2218	0.2241
<i>S</i>	0.605	0.560	0.663	0.472	0.514
No. of reflections used in refinement	3852	3650	2495	7630	7161
No. of parameters used	197	187	198	375	375
H-atom treatment	Isotropic	Isotropic	H atoms placed geometrically, <i>U</i> _{iso} = 1.2 <i>U</i> _{eq} of attached atom	Isotropic	Isotropic
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0322P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0000P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0000P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0000P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0000P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$

Table 1 (cont.)

	(3)	(4)	(5)	(6)	(7)
$(\Delta/\sigma)_{\max}$	-0.009	-0.003	0.009	0.008	-0.022
$\Delta\rho_{\max}$ ($e \text{ \AA}^{-3}$)	0.236	0.315	0.316	0.335	0.426
$\Delta\rho_{\min}$ ($e \text{ \AA}^{-3}$)	-0.266	-0.469	-0.214	-0.243	-0.402
Extinction method	None	SHELXL93 (Sheldrick, 1993)	None	None	None
Extinction coefficient	-	0.0042 (4)	-	-	-
Source of atomic scattering factors	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)
Computer programs					
Data collection	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)
Cell refinement	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)
Data reduction	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)	FAST, MADNES (Pflugrath & Messerschmitt, 1991)
Structure solution	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)
Structure refinement	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)
Preparation of material for publication	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)	SHELXL93 (Sheldrick, 1993)

† Detector-to-crystal distance (DET). ‡ θ = swing angle. § Frame time. ¶ Frame width.

of the refinement, difference maps showed all H atoms for (3), (4), (6) and (7); in the subsequent rounds of refinement the H atoms were positioned on geometrical grounds and refined as riding atoms with isotropic thermal parameters common to all the H atoms attached to the same carbon, and common to the all-phenyl H atoms of a given compound. For structure (5) H atoms were placed geometrically and their temperature factors set to 1.2 times U_{eq} of the respective heavy atom. The trifluoromethyl group appeared to be disordered and it was refined isotropically. F atoms were initially localized on a difference-Fourier map and then refined split into two positions, with almost equal occupancy factors, using *PART* and *EADP* routines of *SHELXL93*. Disorder of the CF_3 group hampered the refinement process.

For most of the samples the crystal quality and size resulted in weak data sets, which has reduced the number of observed reflections considerably. Weak reflections are not well measured on the FAST diffractometer, and this accounts for the high R values when calculated for all data.

A summary of crystal data and processing parameters are given in Table 1. Geometrical calculations were carried out with *PARST* (Nardelli, 1983). Fig. 1 was drawn with *ZORTEP* (Zsolnay, 1995) and Fig. 2 with *SNOOPI* (Davies, 1980).

2.2. Molecular modelling

X-ray determined structures provided the starting geometries for the molecular modelling studies. These

geometries were optimized using the AM1 procedure of *MOPAC* (Stewart, 1989) to generate not only the low-energy geometry of the free molecule, but also the static charges. The positions of all atoms, including H atoms, were optimized using gradient methods and terminated at a gradient of the order $0.419 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$. These new minimized models were then used for conformational searches with the program *ChemX* (Davies, 1993). Throughout all the calculations the geometries of the heterocyclic systems were fixed. In each case the relevant flexible torsion angles were varied [2 for (1), φ_1 and φ_3 , and 3 for all others, $\varphi_1 - \varphi_3$, see (I)] in steps of 20° for $\varphi_1 - \varphi_2$ and by rotation of $6 \times 30^\circ$ for φ_3 . The geometries of all conformations which gave van der Waals energies within $ca 12.6 \text{ kJ mol}^{-1}$ of the starting models were optimized using the molecular mechanics forcefield in *ChemX*.

3. Results and discussion

3.1. X-ray structure analysis

The final atomic coordinates for (3)–(7) are reported in Table 2† and the structural diagrams with atomic numbering of (3)–(6) are shown in Fig. 2. Compounds (6) and (7) are isostructural and the diagrams are

† Lists of atomic coordinates, anisotropic displacement parameters, complete geometry and structure factors have been deposited with the IUCr (Reference: KA0034). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

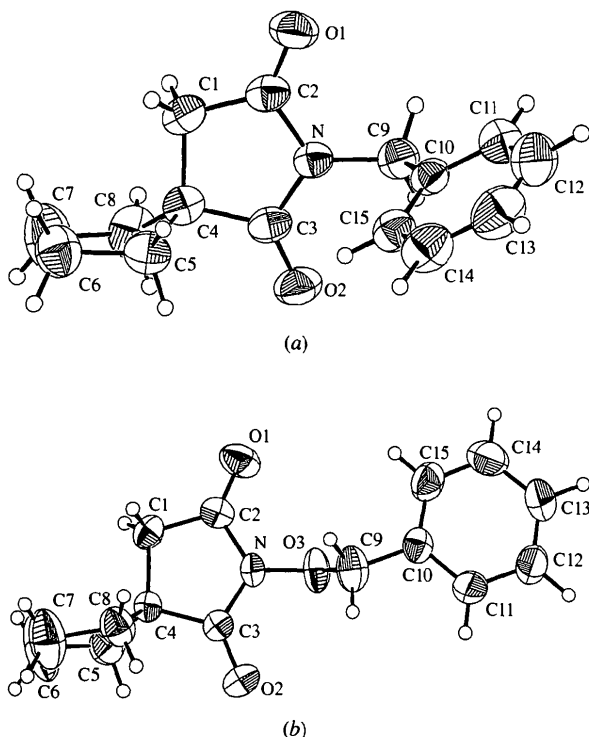


Fig. 1. Molecular conformations in the crystal structure for (1) (panel *a*) and (2) (panel *b*). Thermal ellipsoids are scaled to enclose 50% probability.

indistinguishable to the eye. The latter has therefore been omitted. The packing diagrams are not presented since they have no unusual features. No significant intermolecular contacts are present, the closest distance between H atoms being 2.68 (1) for (3), 2.47 (1) for (4), 2.40 (1) for (5), 2.40 (1) for (6), 2.38 (1) Å for (7), all greater than van der Waals diameter.

The crystals of (6) and (7) contain two crystallographically independent molecules. The translation vector between (6) and (6'), calculated with *PARST* (Nardelli, 1983), has components 0.51 (8), 0.27 (6) and 0.51 (1) along the *a*, *b* and *c* axes, respectively. Molecules (7) and (7') are shifted by almost the same non-crystallographic translation with components 0.51 (9), 0.28 (6) and 0.51 (2). Compounds (3), (4) and (5) have one molecule in the asymmetric unit. Thus, seven independent molecular structures can be compared. The detailed analysis of the molecular geometry, excluding the low-accuracy structure of (5), shows that there is delocalization of electrons from the carbonyl C=O group into the adjacent C—N bonds (see Table 3). These bonds fall within the range 1.364 (4)–1.391 (6) Å and are substantially shorter than the C—N bonds in unsubstituted rings (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The N—O bonds appear to be single and oxygen has sp^3 geometry. Phenyl rings are planar with a maximum atomic deviation of 0.02 (1) Å for the C(15') atom of (7'). The heterocyclic rings with

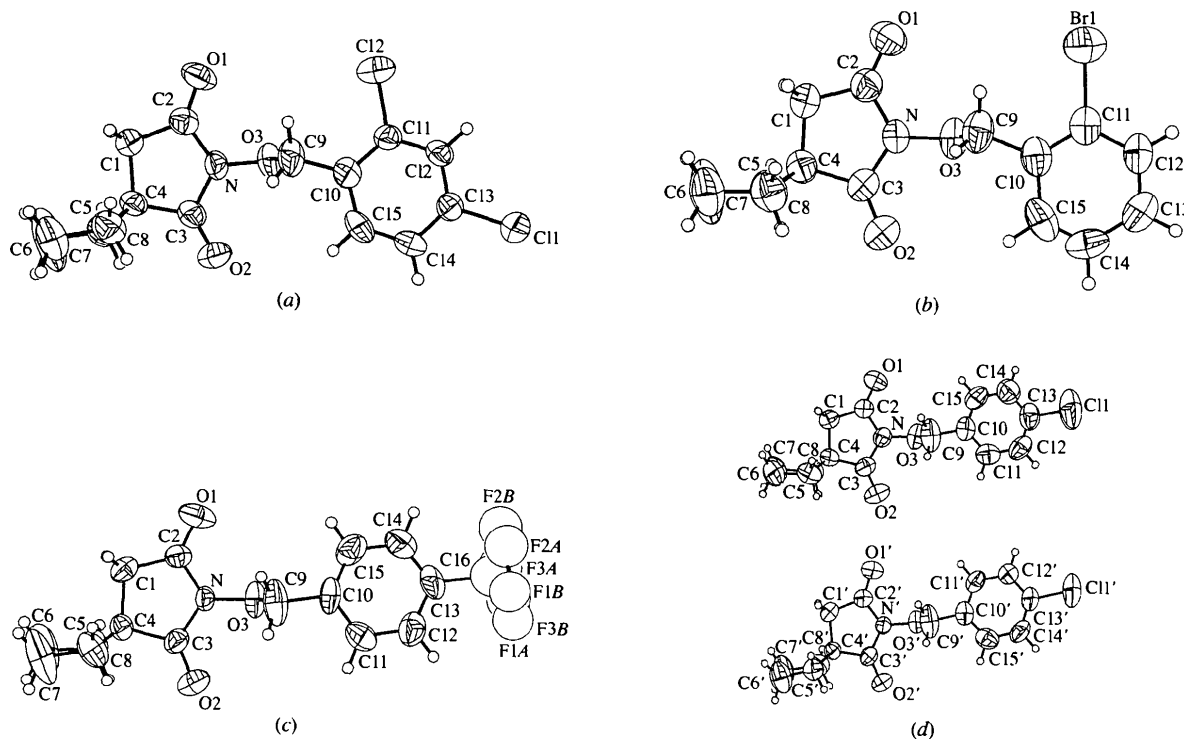


Fig. 2. Molecular conformations in the crystal structure for (3) (panel *a*), (4) (panel *b*), (5) (panel *c*) and (6) (panel *d*), all viewed perpendicular to the plane of the heterocyclic ring. Thermal ellipsoids are scaled to enclose 50% probability.

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA)

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}		<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
(3)					F3B	0.0243 (5)	0.6838 (13)	-0.1239 (17)	0.140 (3)
C5	-0.2658 (2)	-0.4229 (2)	0.0114 (3)	0.0737 (9)	F1A	0.0350 (4)	0.7780 (10)	-0.0768 (16)	0.122 (3)
C6	-0.3719 (3)	-0.4385 (5)	-0.0715 (5)	0.171 (2)	F2A	0.0174 (5)	0.6966 (12)	0.1125 (17)	0.137 (3)
C7	-0.3857 (3)	-0.3727 (3)	-0.2067 (5)	0.1088 (13)	F3A	0.0169 (4)	0.6052 (12)	-0.0931 (16)	0.140 (3)
C8	-0.2849 (2)	-0.3189 (2)	-0.2037 (4)	0.0790 (10)	(6)				
C4	-0.2046 (2)	-0.3813 (2)	-0.0997 (3)	0.0486 (7)	N	0.7150 (3)	0.7998 (2)	0.78093 (12)	0.0610 (8)
C3	-0.1157 (2)	-0.3142 (2)	-0.0309 (3)	0.0571 (7)	C3	0.7917 (5)	0.8285 (3)	0.8252 (2)	0.0726 (11)
O2	-0.1150 (2)	-0.2392 (2)	-0.0453 (3)	0.0938 (8)	O2	0.8778 (4)	0.9033 (3)	0.83060 (13)	0.1227 (13)
N	-0.0292 (2)	-0.35301 (15)	-0.0753 (2)	0.0500 (6)	C4	0.7504 (4)	0.7459 (3)	0.86374 (13)	0.0587 (9)
C2	-0.0436 (2)	-0.4418 (2)	-0.1593 (3)	0.0519 (7)	C1	0.6360 (4)	0.6714 (3)	0.83480 (14)	0.0649 (10)
O1	0.0241 (2)	-0.48752 (14)	-0.2018 (2)	0.0741 (6)	C2	0.6236 (4)	0.7100 (3)	0.78210 (14)	0.0568 (9)
C1	-0.1549 (2)	-0.4661 (2)	-0.1784 (3)	0.0612 (8)	O1	0.5516 (3)	0.6727 (2)	0.74585 (10)	0.0814 (8)
O3	0.06671 (13)	-0.31025 (13)	-0.0276 (2)	0.0613 (5)	C5	0.6955 (5)	0.7971 (4)	0.9100 (2)	0.0838 (13)
C9	0.0881 (2)	-0.2361 (2)	-0.1362 (3)	0.0706 (9)	C6	0.7210 (6)	0.7090 (4)	0.9507 (2)	0.100 (2)
C10	0.1707 (2)	-0.1661 (2)	-0.0590 (3)	0.0535 (7)	C7	0.8362 (6)	0.6309 (4)	0.9328 (2)	0.101 (2)
C11	0.2736 (2)	-0.1743 (2)	-0.0662 (3)	0.0537 (7)	C8	0.8866 (5)	0.6825 (3)	0.8857 (2)	0.0826 (12)
C12	0.3464 (2)	-0.1052 (2)	0.0008 (3)	0.0534 (7)	O3	0.7373 (3)	0.8514 (2)	0.73624 (10)	0.0744 (8)
C13	0.3149 (2)	-0.0253 (2)	0.0787 (3)	0.0504 (7)	C9	0.6316 (6)	0.9391 (4)	0.7272 (2)	0.102 (2)
C14	0.2133 (2)	-0.0147 (2)	0.0930 (3)	0.0591 (8)	C10	0.6492 (5)	0.9776 (3)	0.6754 (2)	0.0696 (11)
C15	0.1428 (2)	-0.0851 (2)	0.0241 (3)	0.0596 (8)	C11	0.7294 (4)	1.0702 (4)	0.6666 (2)	0.0813 (12)
C11	0.40579 (6)	0.06289 (5)	0.16357 (9)	0.0791 (3)	C12	0.7418 (5)	1.1054 (4)	0.6179 (2)	0.0892 (14)
C12	0.31634 (7)	-0.27375 (7)	-0.16384 (11)	0.1095 (4)	C13	0.6793 (6)	1.0456 (5)	0.5794 (2)	0.0936 (15)
(4)					C14	0.6009 (6)	0.9542 (4)	0.5872 (2)	0.108 (2)
C5	0.3906 (2)	0.6809 (5)	0.6038 (6)	0.077 (2)	C15	0.5863 (6)	0.9210 (3)	0.6348 (2)	0.0925 (15)
C6	0.4457 (3)	0.7029 (8)	0.5538 (9)	0.144 (4)	C11	0.7007 (2)	1.0896 (2)	0.51858 (7)	0.1800 (9)
C7	0.4556 (3)	0.6360 (5)	0.4277 (8)	0.100 (2)	N'	0.2186 (3)	0.5216 (2)	0.27390 (10)	0.0497 (7)
C8	0.4059 (2)	0.5705 (5)	0.4038 (7)	0.079 (2)	C3'	0.3032 (4)	0.5560 (3)	0.31553 (14)	0.0570 (9)
C4	0.3615 (2)	0.6322 (4)	0.4727 (5)	0.0590 (11)	O2'	0.3829 (3)	0.6349 (2)	0.31766 (11)	0.0929 (10)
C3	0.3152 (2)	0.5629 (4)	0.5136 (6)	0.0667 (13)	C4'	0.2779 (4)	0.4778 (3)	0.35762 (12)	0.0522 (8)
O2	0.3167 (2)	0.4870 (3)	0.5925 (5)	0.0941 (13)	C1'	0.1588 (4)	0.3992 (3)	0.33343 (14)	0.0646 (10)
N	0.2701 (2)	0.5974 (3)	0.4405 (4)	0.0592 (10)	C2'	0.1337 (4)	0.4302 (3)	0.27999 (14)	0.0559 (9)
C2	0.2759 (2)	0.6900 (4)	0.3641 (5)	0.0618 (12)	O1'	0.0558 (3)	0.3880 (2)	0.24640 (10)	0.0787 (8)
O1	0.2397 (2)	0.7384 (3)	0.3059 (4)	0.0792 (11)	C5'	0.2354 (5)	0.5342 (3)	0.40517 (14)	0.0714 (11)
C1	0.3344 (2)	0.7148 (4)	0.3725 (6)	0.0681 (13)	C6'	0.2968 (6)	0.4622 (4)	0.4474 (2)	0.114 (2)
O3	0.22042 (14)	0.5541 (3)	0.4612 (4)	0.0697 (10)	C7'	0.3998 (6)	0.3820 (4)	0.4276 (2)	0.105 (2)
C9	0.2056 (2)	0.4852 (4)	0.3437 (6)	0.078 (2)	C8'	0.4234 (4)	0.4190 (3)	0.37530 (15)	0.0713 (11)
C10	0.1645 (2)	0.4099 (4)	0.3952 (5)	0.0679 (13)	O3'	0.2276 (3)	0.5693 (2)	0.22759 (9)	0.0613 (6)
C11	0.1111 (2)	0.4121 (4)	0.3573 (6)	0.0691 (13)	C9'	0.1196 (6)	0.6561 (4)	0.2212 (2)	0.098 (2)
C12	0.0763 (2)	0.3370 (4)	0.4090 (6)	0.0741 (15)	C10'	0.1205 (4)	0.6968 (3)	0.16885 (15)	0.0658 (10)
C13	0.0959 (3)	0.2598 (5)	0.4986 (6)	0.082 (2)	C11'	0.0337 (5)	0.6495 (3)	0.1303 (2)	0.0775 (12)
C14	0.1526 (3)	0.2587 (4)	0.5405 (5)	0.076 (2)	C12'	0.0270 (5)	0.6913 (3)	0.0827 (2)	0.0836 (13)
C15	0.1824 (2)	0.3254 (5)	0.4954 (6)	0.078 (2)	C13'	0.1080 (5)	0.7813 (3)	0.07372 (15)	0.0723 (11)
Br1	0.08254 (3)	0.51490 (6)	0.23062 (9)	0.1139 (4)	C14'	0.1967 (5)	0.8299 (3)	0.1103 (2)	0.0827 (13)
(5)					C15'	0.2036 (4)	0.7864 (4)	0.1583 (2)	0.0811 (12)
N	0.2688 (2)	0.4066 (4)	0.0492 (6)	0.0401 (14)	C11'	0.0935 (2)	0.83877 (13)	0.01400 (5)	0.1367 (7)
O1	0.2455 (2)	0.2804 (4)	0.2139 (6)	0.078 (2)	(7)				
O2	0.3073 (2)	0.5102 (5)	-0.1132 (7)	0.103 (2)	N	0.7134 (6)	0.8031 (5)	0.7829 (2)	0.057 (2)
O3	0.22795 (14)	0.4515 (3)	0.0150 (5)	0.0558 (15)	C3	0.7908 (8)	0.8308 (7)	0.8274 (3)	0.068 (2)
C1	0.3229 (2)	0.2914 (5)	0.1500 (8)	0.054 (2)	O2	0.8787 (7)	0.9047 (6)	0.8325 (2)	0.120 (2)
C2	0.2749 (3)	0.3206 (5)	0.1449 (8)	0.045 (2)	C4	0.7531 (7)	0.7475 (6)	0.8643 (2)	0.056 (2)
C3	0.3065 (2)	0.4373 (6)	-0.0195 (8)	0.053 (2)	C1	0.6379 (7)	0.6749 (6)	0.8348 (3)	0.063 (2)
C4	0.3452 (2)	0.3681 (5)	0.0374 (8)	0.048 (2)	C2	0.6244 (7)	0.7122 (6)	0.7837 (3)	0.055 (2)
C5	0.3652 (3)	0.3026 (6)	-0.0884 (9)	0.069 (2)	O1	0.5521 (5)	0.6772 (4)	0.7474 (2)	0.080 (2)
C6	0.4114 (4)	0.2800 (10)	-0.0368 (13)	0.148 (5)	C5	0.6990 (8)	0.7993 (7)	0.9090 (3)	0.079 (2)
C7	0.4238 (3)	0.3691 (10)	0.0716 (15)	0.151 (5)	C6	0.7226 (10)	0.7145 (9)	0.9489 (3)	0.100 (3)
C8	0.3834 (2)	0.4354 (6)	0.1001 (10)	0.079 (3)	C7	0.8388 (10)	0.6355 (9)	0.9328 (3)	0.102 (3)
C9	0.2210 (2)	0.5477 (6)	0.1047 (10)	0.085 (3)	C8	0.8869 (8)	0.6864 (7)	0.8872 (3)	0.081 (2)
C10	0.1740 (2)	0.5828 (6)	0.0804 (9)	0.056 (2)	O3	0.7329 (5)	0.8543 (4)	0.7394 (2)	0.0740 (15)
C11	0.1636 (3)	0.6692 (7)	-0.0144 (9)	0.070 (2)	C9	0.6243 (9)	0.9409 (7)	0.7283 (3)	0.099 (3)
C12	0.1192 (3)	0.7019 (7)	-0.0360 (9)	0.080 (3)	C10	0.6434 (9)	0.9806 (7)	0.6779 (3)	0.065 (2)
C13	0.0857 (3)	0.6485 (8)	0.0348 (9)	0.071 (3)	C11	0.7246 (8)	1.0740 (7)	0.6709 (3)	0.075 (2)
C14	0.0972 (3)	0.5634 (7)	0.1250 (11)	0.090 (3)	C12	0.7399 (8)	1.1093 (8)	0.6239 (4)	0.085 (3)
C15	0.1399 (3)	0.5316 (6)	0.1487 (10)	0.078 (3)	C13	0.6798 (9)	1.0536 (10)	0.5830 (4)	0.096 (3)
C16	0.0358 (4)	0.6857 (11)	0.0049 (18)	0.128 (4)	C14	0.5993 (10)	0.9610 (9)	0.5905 (4)	0.098 (3)
F1B	0.0341 (4)	0.7907 (10)	0.0605 (16)	0.122 (3)	C15	0.5822 (10)	0.9261 (8)	0.6375 (4)	0.093 (3)
F2B	0.0101 (4)	0.6154 (11)	0.0816 (15)	0.137 (3)	Br1	0.70641 (13)	1.10393 (15)	0.52125 (5)	0.1714 (7)

Table 2. (cont.)

	x	y	z	U_{eq}
N'	0.2176 (5)	0.5128 (5)	0.2741 (2)	0.0472 (14)
C3'	0.3025 (7)	0.5501 (6)	0.3157 (3)	0.056 (2)
O2'	0.3788 (6)	0.6311 (5)	0.3164 (2)	0.095 (2)
C4'	0.2849 (6)	0.4716 (5)	0.3560 (2)	0.045 (2)
C1'	0.1661 (7)	0.3922 (6)	0.3330 (2)	0.059 (2)
C2'	0.1362 (7)	0.4199 (6)	0.2807 (3)	0.050 (2)
O1'	0.0606 (5)	0.3758 (4)	0.2465 (2)	0.0746 (15)
C5'	0.2449 (8)	0.5269 (7)	0.4033 (3)	0.072 (2)
C6'	0.3122 (10)	0.4588 (9)	0.4456 (3)	0.112 (3)
C7'	0.4169 (10)	0.3775 (9)	0.4251 (3)	0.105 (3)
C8'	0.4315 (7)	0.4161 (6)	0.3738 (3)	0.064 (2)
O3'	0.2225 (4)	0.5603 (4)	0.2285 (2)	0.0577 (13)
C9'	0.1031 (9)	0.6375 (7)	0.2196 (3)	0.083 (3)
C10'	0.1078 (8)	0.6869 (7)	0.1703 (3)	0.064 (2)
C11'	0.0265 (9)	0.6473 (6)	0.1291 (3)	0.069 (2)
C12'	0.0226 (9)	0.6964 (7)	0.0838 (3)	0.077 (2)
C13'	0.1064 (8)	0.7871 (7)	0.0777 (3)	0.064 (2)
C14'	0.1903 (8)	0.8292 (7)	0.1188 (4)	0.076 (2)
C15'	0.1950 (8)	0.7768 (8)	0.1644 (3)	0.078 (2)
Br1'	0.09562 (13)	0.86119 (10)	0.01848 (4)	0.1260 (5)

two carbonyl O atoms are essentially also planar, with a maximum atomic deviation of 0.09 (1) Å for the C(4) atom of (4). The conformation of the carbocyclic ring in each molecule approximates to an envelope; the largest deviation from the least-squares plane through the C(5), C(6), C(7) and C(8) atoms is 0.07 (1) Å for C(6') of (7). C(4), which defines the flap, lies in the range (taken for all seven considered molecules) 0.53 (1)–0.62 (1) Å out of the same plane.

The most notable feature identified by these studies is the great similarity of the 'extended' type of conformation adopted by all molecules in (3)–(7), irrespective of the form of the phenyl substitution, and which is analogous to that found in unsubstituted (2). This is highlighted in Figs. 1 and 2, in which all molecules are displayed in equivalent orientations. Of particular note is the similarity of each of the torsion angles $\phi_1 - \phi_3$ within (2)–(7), as shown in Table 4. As a result the angle between the plane of the phenyls and heterocyclic rings is 0.2 (1), 2.2 (2) and 5.3 (4)° for active (3), (4) and (5), respectively, and 11.7 (2), 1.7 (2), 12.6 (3) and 1.5 (3)° for inactive (6), (6'), (7) and (7'), respectively. It would therefore seem that even the *ortho*-substitution in the phenyl ring has no marked effect on what would seem to be the preferred conformation. *Ortho*-substitution was also reported to have no effect on the conformation of three arylsemicarbazones studied in the crystal form (Dimmock, Sidhu, Thayer, Mack, Duffy, Reid, Quail, Pugazhenthii, Ong, Bikker & Weaver, 1993).

3.2. Molecular modelling

In order to try to understand the results from the crystallographic studies, molecular mechanics procedures were used to explore the possible flexibility of the molecules. As a result of the calculations described in the *Experimental*, the number of conformations, similar

in energy to the crystal structure conformation, totalled 62 for (1), 148 for (2), 45 for (3), 64 for (4), 143 for (5), 118 for (6) and 152 for (7). The difference in values for (6), compared with (2), (5) and (7), is difficult to understand, but may reflect the fact that a large number of conformers may be bunched around the 12.56 kJ mol⁻¹ cut-off point. Notwithstanding this feature, the results show quite clearly the significant reduction, by *ca* half, of 'acceptable' conformations for *ortho*-substituted derivatives, compared with *para*- or unsubstituted ones. The

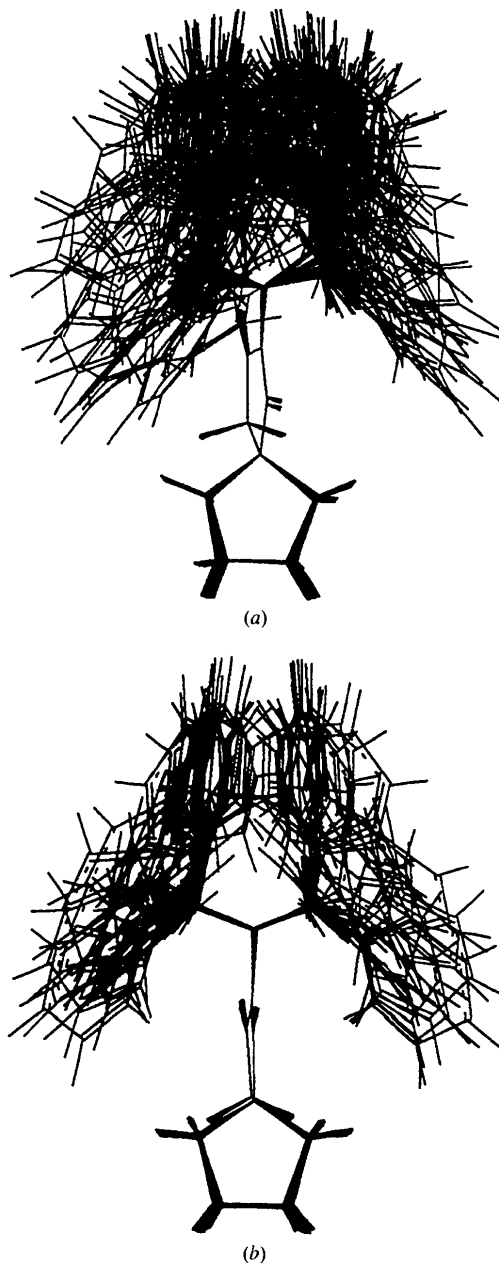


Fig. 3. Superimposed conformationally low-energy structures of (2) (panel a) and (4) (panel b).

Table 3. Selected bond lengths (Å) of (3)–(7)

	(3)	(4)	(5)	(6)	(6')	(7)	(7')
C3—C4	1.507 (3)	1.517 (6)	1.504 (8)	1.519 (5)	1.515 (5)	1.502 (10)	1.484 (9)
N—C3	1.384 (3)	1.366 (6)	1.366 (8)	1.367 (5)	1.364 (4)	1.375 (9)	1.377 (8)
N—C2	1.386 (3)	1.391 (6)	1.360 (8)	1.379 (4)	1.376 (4)	1.381 (8)	1.383 (8)
C1—C2	1.484 (3)	1.494 (7)	1.482 (9)	1.487 (5)	1.483 (5)	1.460 (9)	1.462 (9)
C1—C4	1.537 (3)	1.547 (7)	1.551 (9)	1.538 (5)	1.545 (5)	1.533 (9)	1.535 (8)
C3—O2	1.204 (3)	1.216 (6)	1.225 (7)	1.203 (4)	1.205 (4)	1.208 (8)	1.211 (8)
C2—O1	1.204 (3)	1.206 (6)	1.207 (8)	1.211 (4)	1.211 (4)	1.203 (7)	1.219 (7)
N—O3	1.380 (2)	1.381 (5)	1.366 (6)	1.388 (4)	1.383 (4)	1.370 (6)	1.378 (6)

Table 4. Selected torsion angles (°) of (1)–(7)

	φ_1 C2—N—C9—C10	φ_2	φ_3 N—C9—C10—C11 or N—C9—C10—C15	
(1)	86.4 (2)		-148.5 (2)	34.6 (3)
	C2—N—O3—C9	N—O3—C9—C10	O3—C9—C10—C11 or O3—C9—C10—C15	
(2)	101.7 (3)	-160.1 (2)	-108.7 (3)	71.5 (4)
(3)	90.4 (3)	159.7 (2)	100.3 (3)	-81.1 (3)
(4)	88.2 (5)	157.8 (4)	107.0 (6)	-73.0 (6)
(5)	96.0 (7)	-171.4 (7)	-99.3 (8)	80.2 (9)
(6)	92.3 (4)	-171.6 (3)	-100.5 (4)	79.1 (5)
(6')	94.5 (4)	-173.6 (3)	87.2 (5)	-95.9 (5)
(7)	91.4 (8)	-172.9 (7)	-98.7 (8)	81.0 (9)
(7')	88.8 (7)	-179.1 (6)	94.3 (8)	-86.4 (9)

distribution of the conformations for (2) and (4), as representatives of the *para*-unsubstituted and *ortho*-substituted types are conveniently represented in the 'scatter' plots in Fig. 3, which show quite clearly that the allowed conformations are extensively distributed through conformational space and that for *ortho*-substituted phenyls there are some restrictions due to the steric effects of the *ortho*-substituent hindering slightly rotations about φ_3 . Calculations of the barriers to rotation about this angle show that for the *ortho*-substituted species (3) and (4) they are generally double those for the remainder.

On the other hand, the results also show that throughout the allowed regions, conformations near those found in the crystal are marginally dominant. As mentioned earlier, these conformations all have the extended form of the molecular structure (see Fig. 2).

4. Conclusions

The results of this conformational analysis indicate that reconsideration is necessary of the earlier proposal (Farrar *et al.*, 1993) as to the relationship between conformation and activity. As a result of that earlier work it seemed that, at the molecular structure level, when the mutual orientation of the phenyl-ring connecting bond and the five-membered heterocyclic ring is approximately perpendicular, as in (1), giving a folded conformation, the compound is inactive, whereas if it is extended, as in (2), the compound is active. From our work we find that indeed the activity of (3), (4) and (5) also fits this model, but now we also have two relatively

inactive compounds, (6) and (7), whose structures are also unfolded and have greater flexibility than (3) and (4). It is therefore clear that conformation alone is not decisive in defining activity.

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